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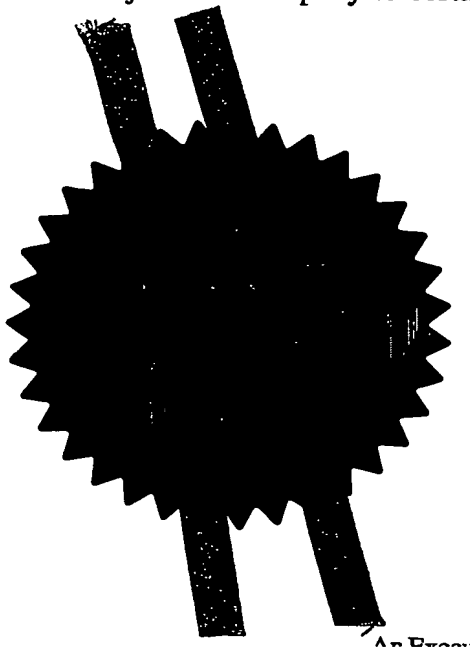

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WOUND MAPPING

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Wound Mapping System

Previous methods

Wound measurement appears to be the only method clinicians have in determining the state of a wound or to assess the effectiveness of a given treatment or dressing, indeed it has been reported that in clinical trials, wound area is the most commonly reported property of wounds[1]. Although current methods are numerous, almost all are simple and most are subjective, bringing their accuracy into question.

The most frequently used techniques are two-dimensional and include linear measurements, wound tracing, planimetry, and stereophotogrammetry.

Linear measurements are perhaps the most simple and involve length and width measurements, taken at the longest length of the wound and the widest width, measured perpendicular to the length axis[2] using a wound gauge or ruler. While clearly quick and inexpensive this method is very subjective and will therefore result in a certain degree of inaccuracy.

A second linear measurement often used in the assessment of wounds is that of area. Several manufacturers to the health care industry have produced a gauge with concentric circles which can be used to estimate wound area. However, as very few wounds will be perfectly circular this method will introduce a large amount of errors into the result. Even in cases where symmetry is evident, subjective identification of the wound boundary can cause inaccuracies in this method.

Planimetry, wound tracing or the acetate method is the technique which employs the use of metric graph paper with a 4cm grid size where the complete squares within the traced wound area are counted and the result indicated in square centimetres[2].

A further 2-dimensional technique used to determine wound parameters is that of stereophotogrammetry, a more complex and expensive method involving the use of a video camera attached to a computer with appropriate software. The wound is captured on video after a target plate has been placed on the plane of the affected area. The target plate allows correct orientation and distortion correction in order to obtain a true image of the wound before it is downloaded to the computer. The wound area can then be traced from the displayed image and the software calculates the wound length, width and area[2]. The improved accuracy of this method and the ability to record results in a database makes it more advantageous than previous techniques but its expense is a limitation.

While a study by Kantor[1] suggests that these methods are *adequate* in determining wound parameters, the need to remove dressings and bandages in order to obtain the measurements remains a crucial shortfall. While there is an obvious necessity to renew and replace dressings from a health point of view, the frequency of replacement can have an effect on the state of the wound. Continual agitation of the wound area does not encourage

healing and removal of adhesive dressings can serve to disrupt the formation of new tissue. Therefore it would be desirable to develop a method of wound measurement which did not require the removal of dressings to calculate the chosen parameters.

An accurate, atraumatic mapping technique would have the very attractive advantage of enabling scientific assessment of the efficacy of various treatments claimed to promote/enhance wound healing and the unequivocal identification of those most effective.

The present invention involves the use of a 'smart dressing' which can be used to monitor aspects of the skin's electrical impedance and thus to assess the size, shape, depth and composition of the wound, all without the need of removing the dressing.

The Healing Process

The skin has several functions including temperature regulation, immunity and protection and when the integrity of the skin is comprised by trauma it is said to be wounded.

Wounds vary in severity and this is gauged mainly by the depth or penetration of the injury and the skin layers involved. Minor abrasions where the portion of skin lost does not extend beyond the epidermis into the dermis is defined as an epidermal wound; while deep wounds are injuries where substantial tissue loss is evident into the lower dermal layers.

The skin's ability to replace itself goes some way to explaining the definition of wound healing. The CREST guidelines on 'Principles of Caring for Patients with Wounds', published in 1998 defines healing in the pathological context as '...the body's replacement of destroyed tissue by living tissue[3]. The onset of an injury triggers a series of cellular and biochemical events from the biological and immunological systems whereby an organised pathway of processes results in a healed wound.

The healing process can be divided into 4 sequential but not distinct phases, haemostasis, inflammation, proliferation and maturation. Haemostasis is the process of stopping bleeding[4] which is a common occurrence in deep tissue trauma; following injury a discharge of blood or fluid from a vessel in the surrounding tissue (extravasation) initiates blood clotting and platelet activation. It is this platelet activation which triggers haemostasis, vasoconstriction and new tissue formation to aid in wound repair. The vasoconstriction is a result of the release of a series of chemical mediators such as histamine, serotonin and adenosine triphosphate (ATP). Their role is to attract the circulating leucocytes (colourless blood component which protects against microorganisms) to the site of impact[4]. The onset of vasoconstriction also coincides with the start of the second or inflammatory phase.

The increased volume of 'local' blood allows plasma to leak to the surrounding tissue thus swelling them, hence inflammation. Neutrophils and monocytes arrive at the wound dormant and on activation the neutrophils set about removing any offensive bacteria while the monocytes become macrophages producing growth factors to accelerate the healing process. Macrophages themselves also phagocytose pathogenic organisms and clear tissue debris.

The last stage of this phase sees the released growth factors stimulating endothelium to oversee the growth of newly formed blood vessels.

The third stage, the proliferation phase is the growth and reproduction of tissue, namely connective or granulation tissue whose formation is dependent on the newly formed blood vessels. The blood vessels provide a suitable environment for tissue regeneration by providing nutrients and oxygen for the cells. Firstly fibroblasts create a network of collagen fibres in the wound bed and produce a sticky substance, proteoglycan which fills the tissue bed binding the fibres together to form a stable framework. Epithelialisation and contraction are the final processes in this stage whereby the wound regenerates epithelium from the outer edges of the wound towards the centre. The cells migrate across the surface to they meet and at the same time the wound is contracted by myofibroblasts.

The fourth and final phase of the healing process is the maturation phase which can be several weeks from the time of injury and involves the remodelling of the collagen fibres laid down in the proliferation phase[4]. This collagen is soft and gelatinous and is replaced in this stage by more orderly and stronger collagen. The final act in the healing process is the removal of fibroblasts from the wound site and the restructuring of blood vessels away from the area which results in the shrinking and paling of the scar tissue[4].

The Skin and its Electrical Properties

The skin is made up of 3 main layers: - the subcutaneous layer, the dermis, and the epidermis (the strongest layer)[5].

The epidermis, the outermost layer, is in direct contact with the environment and therefore provides a protection barrier to outside materials (products, water, etc.) as well as filtering sunlight. Unlike any other organ of the body, the epidermis is self-renewing and hence replaces itself continually[6].

The epidermis can be sub-divided into several further layers with the stratum corneum forming the outermost layer. Cells in the underlying basal layer are constantly multiplying and undergo changes as they push up towards the skin's surface. As these cells become flattened, compacted and dehydrated, they lose their nuclei and develop a hardening protein, eventually forming the stratum corneum. The dead cells on the surface are continuously being shed, replaced by the cells migrating from the underlying layers[7].

The stratum corneum consists of several layers of dead cells and varies in thickness depending on location on the body, the thickest layers being on the palms of the hand and the bottom of the feet. The stratum corneum becomes thicker with age and exposure to the elements making it more susceptible to wrinkles and creases[5].

The relatively non-conductive stratum corneum sandwiched between a conductive electrode interface, and the conductive hydrated underlying tissue, acts as a dielectric between two plates as in a capacitor. Therefore the stratum corneum's electrical properties is often represented by a simple capacitor, C_P[8].

Some ions do however traverse the stratum corneum barrier and this is represented, along with the capacitance, by a large parallel resistance, R_P.

The tissues underlying the skin are conductive and can be represented by a resistance, R_T, in series with the above parallel combination[9]. The equivalent circuit model is shown in figure 1. This equivalent circuit model comprising simple resistances and a capacitance is obviously a simplification of the skin's complex electrical properties.

At very high frequencies, the impedance of the capacitance tends to zero and the overall impedance approaches that of R_T. At low frequency the impedance of the capacitance tends to infinity and current therefore flows through the series combination of R_T and R_P and the overall impedance is generally therefore much larger than the high frequency case.

Complex Impedance Plot of Skin Impedance:

Theoretically the impedance locus of the 'classical' model (equivalent circuit incorporating a resistance and capacitance in parallel) should consist of a semi- circular arc whose centre is located exactly on the real axis, as shown on figure 2.

However, Figure 3 shows the typical form of a measured impedance locus plot of the electrode–skin interface, demonstrating that the simple model described above is not adequate to fully characterise the electrical properties of the skin.

R_∞ and R_o, the intercepts with the real axis at high and low frequencies respectively, are the high and low frequency limit resistances. The depression of the centre of the arc below the axis, is expressed in terms of the angle ϕ. ω_o ($=2\pi f_o$) is the angular velocity of the 'peak' of the arc. This is the point with the largest value of reactance, X_C[6].

Impedance loci such as the one above have been found to be well modelled by the formula derived by Cole in 1940[10] (equation1). [Other mathematical models are possible].

$$Z = R_\infty + (R_0 - R_\infty)/[1 + j\omega/\omega_0)^\alpha] \qquad (1)$$

The expression is used to describe the complex impedance of certain biological tissues. α is dimensionless and has a value $0 < \alpha \leq 1$ and is related to ϕ such that $\phi = \alpha\pi/2$. When $\alpha=1$, the impedance locus is a semi-circular arc whose centre lies on the real axis with a frequency intercept angle ϕ of 90°. When $\alpha<1$, as is normally the case, the locus takes the form of a 'depressed' semi-circular arc whose centre lies below the real axis and the frequency intercept angle ϕ is less than 90°.

The complex impedance described by the Cole equation (1) corresponds to several equivalent circuits. Figure 4 shows one such circuit favoured by the author.

Z_{cpa} is an empirical, constant phase angle impedance which shunts the resistance R_p where :

$$Z_{cpa} = K(j\omega)^{-\alpha} \quad (2)$$

K is a measure of the magnitude of Z_{CPA} (i.e. $K = |Z_{CPA}|_{\omega=1}$) and has units of $\Omega\ s^{-\alpha}$. These circuit elements can be expressed in terms of the Cole parameters R_∞, R_0, ω_0 and α, as follows:

$$R_p = (R_0 - R_\infty) \quad (3)$$

$$K = (R_0 - R_\infty)/T_0^{-\alpha} = Rp/T^{-\alpha} \quad (4)$$

$$R_T = R_\infty \quad (5)$$

Invention

It can be readily appreciated that when the stratum corneum at a given skin site is punctured, abraded or absent (as a consequence of trauma or disease, for example) the measured low-frequency impedance at the site will be dramatically reduced due the absence of the large stratum corneum impedance (represented in the simplest case (Figure 1) by the parallel combination of the skin's capacitance and resistance, C_P and R_P). Only the small resistance, R_T, of the underlying tissue will remain.

Mapping, for example, the low-frequency impedance of skin sites in and around a wound site will evidence clearly the major differences between healthy skin (high impedance) and the wound (low impedance).

If an array of electrodes is located over the wound site (Figure 5), the impedances of the individual electrodes can be used to create a two dimensional map of the wound. If a sufficient number of small area electrodes are used, the shape and size of the wound can be ascertained from the measured impedance values. Over time, changes in the wound shape and size can be followed using this technique.

It is possible to model the electrical properties of tissues with equivalent electrical circuits. With the correct choice of mathematical or equivalent circuit model, it is possible to relate the model elements to the underlying physical processes and thus study the healing processes and meaningfully assess the efficacy of a range of therapies.

The use of a multi-electrode array will enable the monitoring of different sites without the need to move a single electrode from one measurement site to the next.

Hydrogel is presently used as a wound dressing as it protects the wound bed from foreign contaminants, and hydrates and enhances the environment essential to thorough wound healing. Hydrogels can also be used in the construction of bio-impedance monitoring electrodes and, along with the use of screenprinting or similar technologies, lend themselves

to the fabrication of accurate, flexible, low-profile electrode arrays. The patterned electrodes can therefore be incorporated into the hydrogel-based wound dressing and used to monitor the wound and the effect of therapy without the need to remove the dressing. A significant improvement on current techniques is that this system does not interfere with the wound bed. As the system is designed to be used as part of the dressing or to constitute the dressing, it allows new tissue formed as part of the healing process, to remain undisturbed while the wound is being assessed. In addition to calculating the wound area, this device is also effectively assisting wound healing.

Most of the prior art discussed above produce wound parameters like length and width and at best volume values, but none, with the exception of the stereophotogrammetry, produce a map or picture of the wound. Even using stereophotogrammetry the wound parameters must be calculated from the picture after the wound photograph has been 'traced' around using the computer. This method can be inaccurate due to the difficulties associated with capturing a real size image of the wound to download.

In one embodiment, this invention aims to map the wound direct from the site and produce an image, complete with calculations of area, tissue type etc., on a computer screen with little involvement from the clinician required, therefore reducing subjectivity and error.

As a wound heals, particularly a full thickness wound, it passes through several phases or stages where new tissue and eventually skin will form. Therefore another indication of wound healing is the tissue type present in the wound bed. It is possible to model the electrical properties of tissues with mathematical and/or equivalent electrical circuits. With the correct choice of mathematical or equivalent circuit model, it is possible to relate the model elements to the underlying physical processes and thus study the healing processes and meaningfully assess the efficacy of a range of therapies.

The proposed 'smart dressing' therefore characterises tissue and hence evaluates the tissue type present under the individual electrodes incorporated in the dressing. This information can then be used to establish the state of the wound.

Due to the severity of some full thickness wounds, many sores will not heal without some form of intervention. Several treatment techniques are employed the use of drugs, wound dressings and the application of electrical signals. Any affect that these techniques have on wound healing can ideally be assessed using electrical impedance spectroscopy (EIS). The application of electrical fields (DC, pulsed, etc.) has been reported to promote wound healing[11,12,13]. Unfortunately, due to the difficulties in assessing wound healing, it has not been possible to establish clearly the best 'electrical therapy'. This shortcoming can be addressed with the use of the impedance array as the electrodes can be used to apply the desired 'electrotherapeutic' signals and to evaluate their effects, all without removing the dressing. The electrodes can also be used for iontophoretic drug delivery and assessment of resultant therapeutic effect or tissue trauma.

Electrode Array Fabrication

The electrode array would best be fabricated using screenprinting or related techniques, thus enabling the accurate patterning and positioning of the electrodes and their associated leads. Optimally, the leads should be patterned using conductive materials such as serigraphic silver-loaded inks. The impedance recording electrodes are optimally formed using serigraphic silver/silver chloride - loaded inks to ensure good electrical performances at the electrode-gel interface. Other materials may be used if the electrodes are to also apply iontophoretic or other therapeutic electrical signals.

An insulating layer should be deposited over segments of connecting leads to avoid electrical shorting.

The array would best be patterned on to a suitable, thin, flexible substrate.

The substrate can be one continuous sheet or be perforated or cut into 'finger-like' peninsulas to enhance flexibility and enable moisture to escape, where necessary.

A backing of suitable material can be used, if necessary, to hold the 'finger-like' peninsulas together and ease application.

A hydrogel would best be used as the electrode gel as hydrogels are well tolerated by the skin and are currently used in wound dressings. A single sheet of hydrogel can be used to cover all the electrodes and the wound or individual hydrogel 'pads' can be placed over the electrodes. In the case of a single sheet, electrodes and their respective gel can effectively be separated from each other by rendering intervening sections of the hydrogel relatively non-conductive. This can be achieved during the manufacture of the hydrogel or by treating the hydrogel sheet with, for example, heated blades which selectively dry portions of the hydrogel sheet.

Obviously, the more electrodes in the array the better resolution. The optimum number will depend on the given application, the size of the wound under study and the mapping accuracy required. A typical range is between 5 x 5 and 100 x 100 array of electrodes depending on application and wound size. For certain routine clinical monitoring applications as few as two measuring electrodes may be sufficient. Typical electrode sizes range from 1mm x 1mm to 1cm x 1cm.

Electrode Technique: 2-, 3- or 4-electrode

A range of electrode arrangements are possible for impedance measurement. The best will depend on the given application.

If the same two electrodes are used to 'inject' the current and to measure the resultant voltage (or vice versa), this is termed the 2-electrode technique. In this case, the impedances

of the two electrode-skin interfaces are measured in series with that of the underlying tissue between them.

A 4-electrode technique involves injecting current via a different pair of electrodes to those used to detect the voltage. In theory this avoids contributions from the 4 electrode-skin interfaces and one should therefore optimally observe the properties of the tissue between the voltage detecting electrodes.

A 3-electrode technique exists which enables one to study the properties of an individual interface without contributions from the other electrodes or the bulk of the sample. This technique is ideally suited to study the impedance of one single electrode-skin site.

Based on the above, the preferred electrode technique for wound mapping is the three electrode technique. This involves the use of a test electrode through which an alternating current is passed and a 'back' electrode (usually positioned on the opposite side of the body segment under investigation) used to complete the current loop (Figure 6). A 'reference' electrode positioned directly beside the test electrode senses the potential, V1 across the electrode-skin impedance under test and the input potential, ΔV to the voltmeter can hence be calculated (equation 6).

$$\Delta V = V1 + V12 + V2 = I_1 Z_{el\_sk1} + I_2 Z_{dermis12} + I_2 Z_{el\_sk2} \qquad (6)$$

If a voltmeter is used which contains an instrumentation amplifier with an extremely high input impedance the result will be a negligibly small current, I_2, flowing through $Z_{dermis12} + Z_{el\_sk2}$. Therefore the voltage difference, ΔV, is equal to the voltage drop, V1 across the test electrode-skin impedance under investigation, as the voltages V12 and V2 measured across the tissue impedance and the site below the reference electrode respectively are also negligible. The electrode-skin interface impedance is obtained by dividing the measured voltage drop, ΔV, by the applied current, I.

In one embodiment of the invention, the 'reference' electrodes for each 'test' electrode in the array can be merged together to form thin, continuous strips as shown in Figure 7. This arrangement has the advantage of not requiring changes in connection to the 'reference' electrodes while impedance measurements are carried out from one test electrode in the array to another. A further advantage is that the long fine amalgamation of the reference electrodes takes up less space on the electrode array, thus maximising the surface covered by test electrodes in the array.

Although the 'back' electrode is generally best positioned on the opposite side of the body site under investigation, it can be incorporated into the array for ease of use. In this case it can be, for example, a long electrode around the peripheral edge of the array.

The 'test' electrodes forming the arrays may be rectangular, circular or any other form which is best suited for a given application and which lends itself best to the fabrication technique. The distribution of the 'test' electrodes in the arrays may be regular or irregular, as required by the given application and algorithms used.

The layout of electrodes within an array can be 'rectangular' (as in Figure 7) or a series of concentric circles (Figure 8a). Individual test electrodes can be arranged in a circular pattern as illustrated in Figures 8b and 8c. In Figure 8a the concentric circular 'test' electrodes can be interspaced by circular 'reference' electrodes. In Figure 8b the 'reference' electrodes form the 'spokes of a wheel' whereas in Figure 8c they form concentric circles. Obviously many permutations are possible.

On Figure 8 the leads to the 'test' and 'reference' electrodes are not shown for clarity. Connecting leads can be either be (i) interlaced around other electrodes, (ii) deposited in layers interspaced with dielectric insulating layers to enable the crossing over of the leads without electrical shorting or, (iii) 'through-hole-plated' to the reverse side of the substrate so that the leads avoid the side with the deposited electrodes.

An advantageous feature of the invention is the possible use of the 4-electrode technique by appropriate connection to sets of any four electrodes in the array. The 4-electrode technique enables the study of the underlying tissue impedance and can be used to assess the tissue within the wound. Inter-electrode distances influence the depth the electric field penetrates into the tissue and hence these can be chosen to study differing depths of the wound. In electrode arrays incorporating many small area electrodes, combinations can be chosen to study and map the wound site for a range of penetration depths.

Measurement Signal

Obviously a suitably wide frequency range (typically from MegaHertz to milli-hertz) should be used and a sufficiently large number of data points obtained if a complete characterisation is required for research purposes. For routine clinical use of the invention, one or several strategically chosen frequency measurements may be all that is required for a given application. The applied signal amplitude for impedance measurement should be such as to ensure that the resultant current density is low, ensuring electrical safety and skin impedance linearity.

Calculation and presentation of impedance parameters

For research purposes, for example, to study the effects of electromagnetic fields on wound healing, one may be interested in measuring the skin or tissue impedances over a wide frequency range using numerous frequencies. Maps of the calculated parameters of mathematical models (e.g. Cole equation (equation 1)) or equivalent circuit models (e.g. Figure 4) may then be presented on a monitor screen or printed for records. Alternatively, for example, the areas of specific regions as revealed by impedance parameters, ratios of parameters or other calculations involving such parameters may be calculated and presented, dispensing with the need to present, inspect and interpret maps.

Maps of calculations based on the following can be used to highlight difference regions in the wound site and differences in the tissues involved:

(i) Magnitude of the impedance (or admittance or similar electrical property) (modulus, real and imaginary components) and phase angle measured at a given frequency.

(ii) Ratios of the above where two or more such measurements are carried out at different frequencies. Other mathematical calculations are also possible.

(iii) Mathematical model parameters (e.g. Cole model) and ratios or other mathematical calculations involving such parameters.

(iv) Equivalent circuit parameters and ratios or other mathematical calculations involving such parameters.

For intact skin, the impedance measured at a low frequency is dominated by the skin impedance rather than that of the underlying tissue. Maps of a wound site can therefore be simply obtained by mapping the site impedances measured at one single frequency, thus greatly simplifying the procedure.

If, based on research, only one model parameter is of interest for a given application, only two or three measurement frequency points will be required. For example, the calculation of K, α and Rp in the equivalent circuit model shown in Figure 4 will require the use of at least two frequencies, more if high accuracy is required.

Miniaturisation

Miniaturised electronics can be mounted on the wound dressing to apply any therapeutic waveforms (e.g. iontophoresis or 'electric wound' healing) and detect the impedance (or related) properties.

Such miniaturised, low profile and (preferably) flexible devices can also be used to display (e.g. via an LED display) key parameter values associated with healing, trauma etc., thus providing important information in a clinical setting.

Displayed information can be in the form of alpha-numerics, colour coding or other data forms to indicate degrees of severity, depth, tissue type or other associated parameters.

The miniaturised electronics can be reusable, hence clipping on or connecting to the electrode array, or preferably disposable along with the array.

Other applications

The impedance array can be used to study the electrical properties of other organs/structures such as the heart or brain. Arrays of very small electrodes (e.g. in the micrometer range) can be fabricated using thin film techniques onto flexible substrates. In the case of the heart, areas of ischaemia may be detected, characterised and mapped using this invention.

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FIGURES

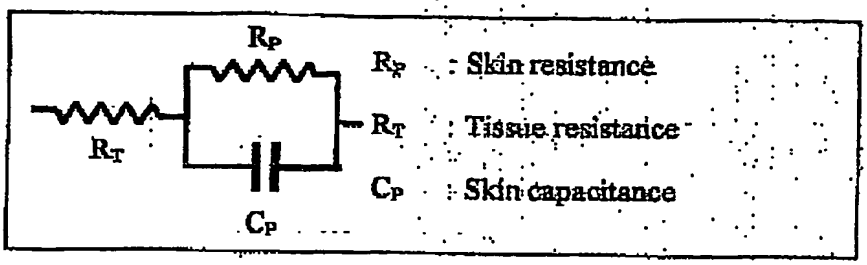

Figure1. Simple equivalent circuit model of the Skin at a given site

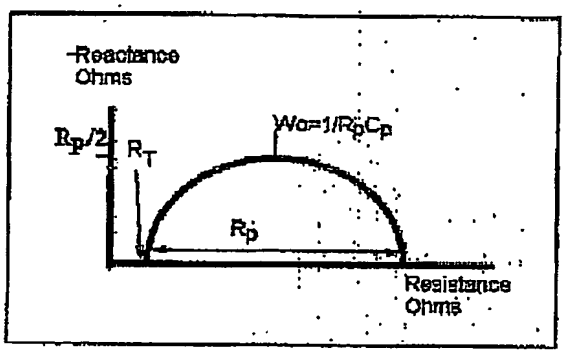

Figure 2. Complex impedance locus for the Simple equivalent circuit model of the Skin

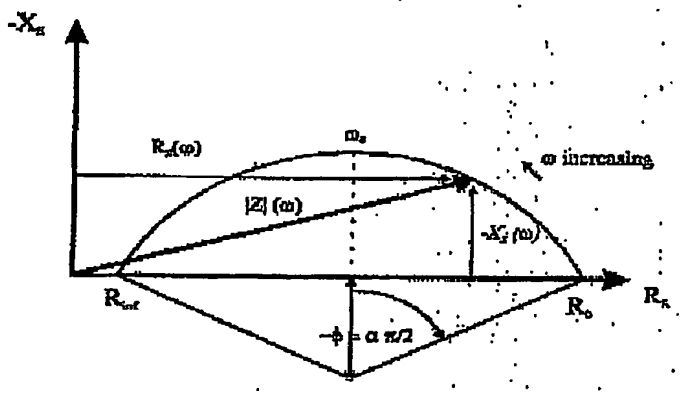

Figure 3. Typical form of measured complex impedance locus for Skin

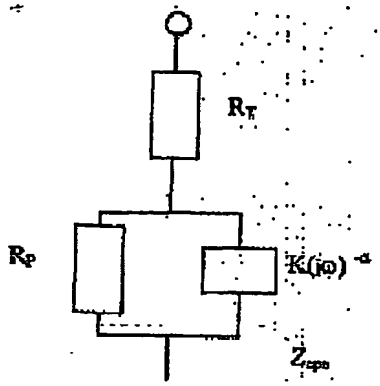

Figure 4: Possible Skin Impedance Model

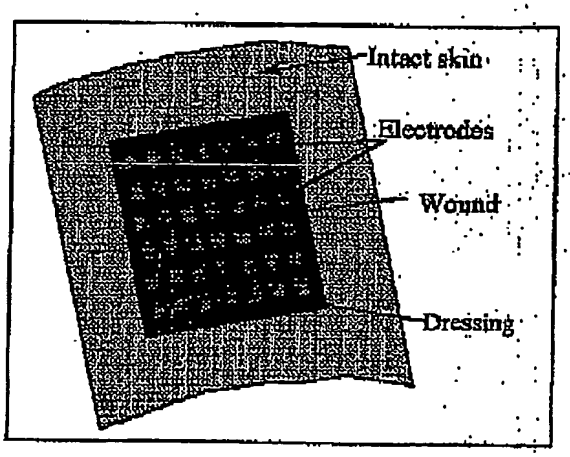

Figure 5: Schematic representation of electrode array to assess wounds (leads are not shown)

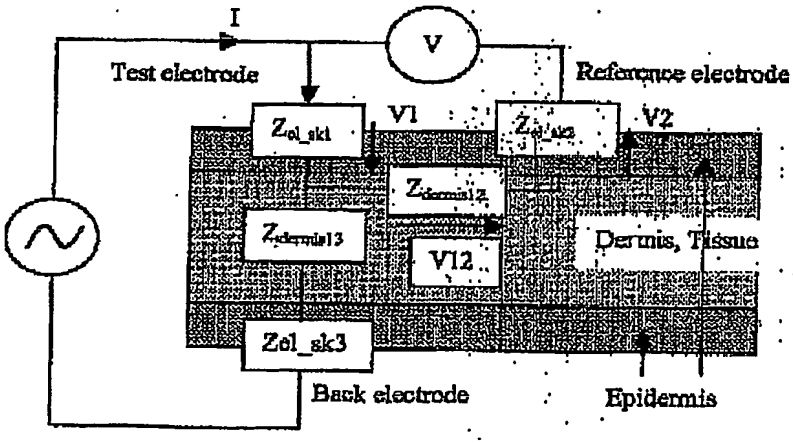

Figure 6. 3-electrode technique

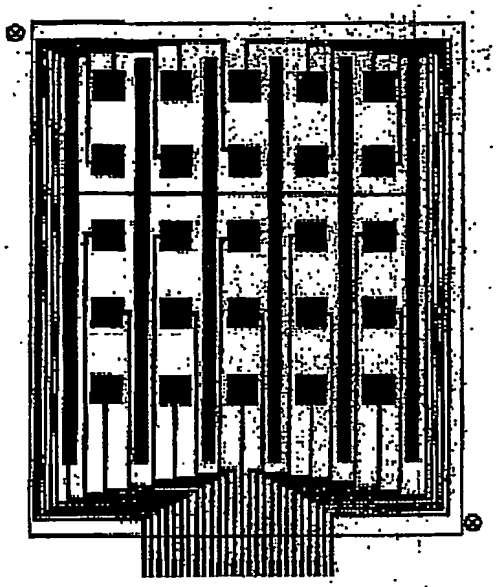

Figure 7. Schematic diagram of a possible Electrode Array

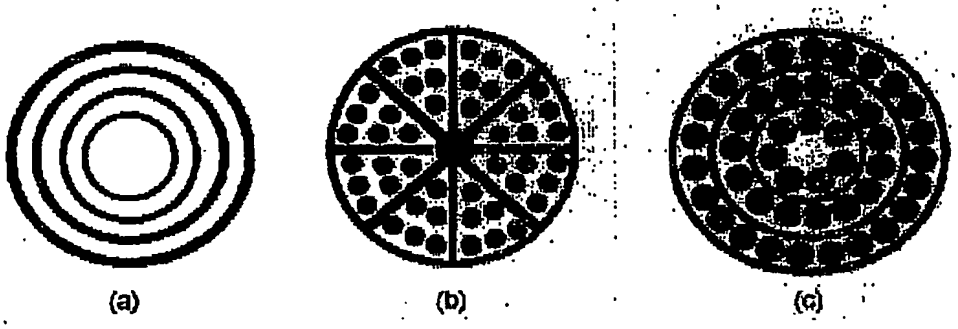

Figure 8. Schematic of possible designs of electrode array (without tracks and connections) (a) concentric circles (b) 'wheel effect' (c) circular